FORM PTO-1390 (Modified) (REV 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: **218199US0PCT**

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR): **10/031490**

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/06540	**10 July 2000**	**20 July 1999**

TITLE OF INVENTION
COMBINED PREPARATIONS COMPRISING ANTITUMOR AGENTS

APPLICANT(S) FOR DO/EO/US
GERONI Cristina

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include itens (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☐ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

Notice of Priority/Form PTO-1449
Application Data Sheet (3 pages)
PCT/IB/304
PCT/IB/308

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
10/031490	PCT/EP00/06540	218199US0PCT

24. The following fees are submitted:.		CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :			
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO	**$1040.00**		
☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO	**$890.00**		
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	**$740.00**		
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)	**$710.00**		
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)	**$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =		**$890.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).		**$130.00**	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	- 20 =	0	x $18.00	**$0.00**	
Independent claims	- 3 =	0	x $84.00	**$0.00**	
Multiple Dependent Claims **(check if applicable)**.			☐	**$0.00**	
TOTAL OF ABOVE CALCULATIONS			=	**$1,020.00**	
☐ Applicant claims small entity status. See 37 CFR 1.27). The fees indicated above are reduced by 1/2.				**$0.00**	
SUBTOTAL			=	**$1,020.00**	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).			+	**$0.00**	
TOTAL NATIONAL FEE			=	**$1,020.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐				**$0.00**	
TOTAL FEES ENCLOSED			=	**$1,020.00**	
				Amount to be: refunded	$
				charged	$

a. ☒ A check in the amount of **$1,020.00** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **15-0030** A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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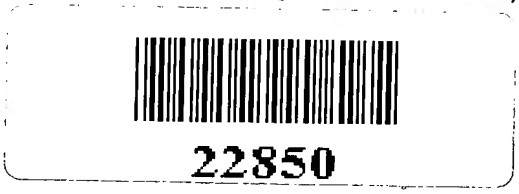
Registration No. 34,423



Surinder Sachar
SIGNATURE

Norman F. Oblon
NAME

24,618
REGISTRATION NUMBER

Jan 22 2002
DATE

218199US-0PCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF :

CRISTINA GERONI ET AL : ATTN: APPLICATION DIVISION

SERIAL NO: 10/031,490 :

FILED: JANUARY 22, 2002 :

FOR: COMBINED PREPARATIONS COMPRISING ANTITUMOR AGENTS

PRELIMINARY AMENDMENT

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

Prior to examination on the merits, please amend the above-identified application as follows.

IN THE CLAIMS

Please amend the claims as shown on the marked-up copy following this amendment to read as follows:

3. (Amended) Products according to claim 1, wherein the alkylating anthracycline is 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin.

4. (Amended) Products according to claim 1, wherein the antitumor therapy is for treating cancers over-expressing HER2 protein.

REMARKS

Claims 1-14 are active in the present application. Claims 3 and 4 have been amended to remove multiple dependencies. No new matter is added. An action on the merits and allowance of claims is solicited.

Respectfully submitted,

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218199US-0PCT

Marked-Up Copy
Serial No:
10/031,490
Amendment Filed on:
05/10/02

IN THE CLAIMS

--3. (Amended) Products according to claim 1 [or 2], wherein the alkylating anthracycline is 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin.

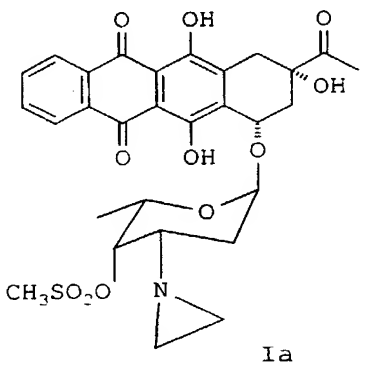
4. (Amended) Products according to [any one of claims 1 to 3] claim 1, wherein the antitumor therapy is for treating cancers over-expressing HER2 protein.--

Title: "Combined preparations comprising antitumor agents"

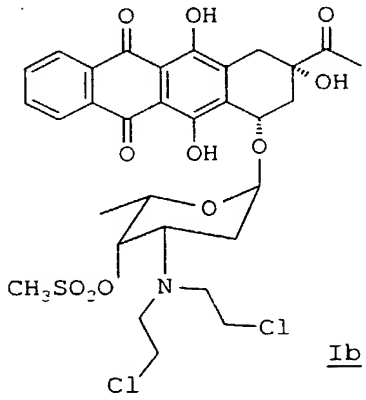
The present invention pertains to the field of neoplastic disease therapy. Particularly, this invention provides an antitumor composition comprising an alkylating anthracycline and a recombinant humanized anti-HER2 antibody, for example the recombinant humanized monoclonal antibody (rhuMab) anti-HER2, trastuzumab (Herceptin™), having a synergistic or additive antineoplastic effect.

The present invention provides, in a first aspect, a pharmaceutical composition for use in antineoplastic therapy in mammals, including humans, comprising

- an alkylating anthracycline of formula Ia or Ib



Ia



Ib

- a recombinant humanized anti-HER2 antibody and a pharmaceutically acceptable carrier or excipient.

The recombinant humanized anti-HER2 antibody is preferably, the recombinant humanized monoclonal antibody anti-HER2 trastuzumab.

The chemical names of the alkylating anthracyclines of formula Ia and Ib are 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin (Ia) and 4-demethoxy-N,N-bis(2-chloroethyl)-4'-methansulfonyl daunorubicin (Ib). These alkylating anthracyclines were described in Anticancer Drug Design (1995), vol. 10, 641-653, and claimed respectively in US-A-5,532,218 and US-A-5,496,800. Both compounds intercalate

into DNA via the chromophore and alkylate guanine at N^7 position in DNA minor groove via their reactive moiety on position 3' of the amino sugar. Compounds Ia and Ib are able to circumvent the resistance to all major classes of cytotoxics, indicating that the compounds represent a new class of cytotoxic antitumor drugs.

The recombinant humanized monoclonal antibody anti-HER2 trastuzumab (Herceptin™) is described in various scientific publications, for example Cancer Res., 1998, 58:2825-2831.

The present invention also provides a product comprising an alkylating anthracycline of formula Ia or Ib as defined above and a recombinant humanized anti-HER2 antibody, preferably the recombinant humanized monoclonal antibody anti-HER2 trastuzumab, as combined preparation for simultaneous, separate or sequential use in antitumor therapy.

A further aspect of the present invention is to provide a method of treating a mammal, including a human, suffering from a neoplastic disease comprising administering to said mammal an alkylating anthracycline of formula Ia or Ib as defined above and a recombinant humanized anti-HER2 antibody, preferably the recombinant humanized monoclonal antibody anti-HER2 trastuzumab, in amounts effective to produce a synergistic antineoplastic effect.

A still further aspect of the present invention is to provide a method for lowering the side effects caused by antineoplastic therapy with an antineoplastic agent in a mammal, including a human, in need thereof, the method comprising administering to said mammal a combined preparation comprising an alkylating anthracycline of formula Ia or Ib as defined above, and a recombinant humanized anti-HER2 antibody, preferably the the recombinant humanized monoclonal antibody anti-HER2 trastuzumab, in amounts effective to produce a synergistic antineoplastic effect.

By the term "a synergistic antineoplastic effect" as used herein is meant the inhibition of the growth tumor, preferably

the complete regression of the tumor, administering an effective amount of the combination of an alkylating anthracycline of formula Ia or Ib as defined above and a recombinant humanized anti-HER2 antibody to mammals, including humans.

By the term "administered" or "administering" as used herein is meant any acceptable manner of administering a drug to a patient which is medically acceptable including parenteral and oral administration. By "parenteral" is meant intravenous, subcutaneous and intramuscular administration. Oral administration includes administering the costituents of the combined preparation in a suitable oral form such as, e.g., tablets, capsules, suspensions, solutions, emulsions, powders, syrups and the like. Parenteral administration includes administering the costituents of the combined preparation by subcutaneous, intravenous or intramuscular injections.

The actual preferred method and order of administration of the combined preparations of the invention may vary according to, inter alia, the particular pharmaceutical formulation of the alkylating anthracycline of formula Ia or Ib as defined above being utilized, the particular pharmaceutical formulation of the recombinant humanized anti-HER2 antibody being utilized, the particular cancer being treated, and the particular patient being treated.

The dosage ranges for the administration of the combined preparation may vary with the age, condition, sex and extent of the disease in the patient and can be determined by one of skill in the art.

The dosage regimen must therefore be tailored to the particular of the patient's conditions, response and associate treatments in a manner which is conventional for any therapy, and may need to be adjusted in response to changes in conditions and/or in light of other clinical conditions.

In the method of the subject invention, the alkylating anthracycline may be administered simultaneously with the

recombinant humanized anti-HER2 antibody, or the compounds may be administered sequentially, in either order.

In the method of the subject invention, for the administration of the alkylating anthracycline of formula Ia or Ib as defined above, the course of therapy generally employed is from about 0.1 to about 200 mg/m^2 of body surface area. More preferably, the course therapy employed is from about 1 to about 50 mg/m^2 of body surface area.

In the method of the subject invention, for the administration of the recombinant humanized anti-HER2 antibody, for example for the administration of the recombinant humanized monoclonal antibody anti-HER2 trastuzumab, the course of therapy generally employed is from about 1 to about 1000 mg/m^2 of body surface area. More preferably, the course therapy employed is from about 50 to about 500 mg/m^2 of body surface area.

The antineoplastic therapy of the present invention is, in particular, suitable for treating breast, ovary, lung, colon, kidney, stomach, pancreas, liver, melanoma, leukemia and brain tumors in mammals, including humans. More in particular, the combined use of an alkylating anthracycline according to the invention and a recombinant humanized anti-HER2 antibody, for example the recombinant humanized monoclonal antibody anti-HER2 trastuzumab, can be suitable for the treatment of patients with cancers over-expressing the HER2 protein, for example, for patient with metastatic breast cancer over-expressing the HER2 protein.

The antineoplastic therapy according to this invention also comprises the prevention and/or treatment of tumor metastasis.

A still further aspect of the present invention is the use of an alkylating anthracycline of formula Ia or Ib as defined above and a recombinant humanized anti-HER2 antibody, preferably the recombinant humanized monoclonal antibody anti-HER2 trastuzumab, for the treatment of tumors by angiogenesis inhibition.

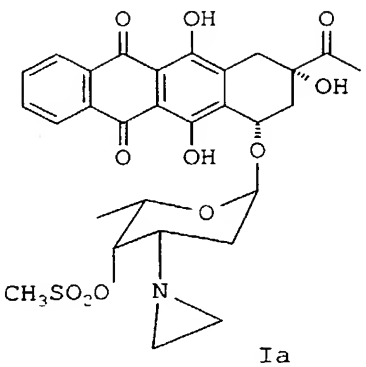
As stated above, the effectiveness of an alkylating anthracycline of formula Ia or Ib and a recombinant humanized anti-HER2 antibody is significantly increased without a parallel increased toxicity. In other words, the combined therapy of the present invention enhances the antitumoral effects of the alkylating anthracycline of formula Ia or Ib as defined above and of a recombinant humanized anti-HER2 antibody and thus yields the most effective and least toxic treatment for tumors.

The synergistic action displayed by the combined preparations according to the present invention can be shown, for instance, by testing the activity of the combination in mice bearing human tumor xenografts overexpressing HER2 protein, following, for example, the method described in Cancer Research, 1998, 58:2825-2831.

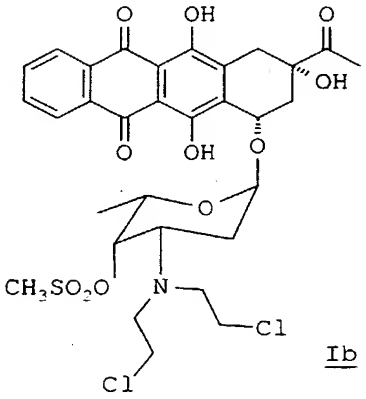
Suitable modifications and adaptations of a variety of conditions and parameters normally encountered in clinical therapy which are obvious to those skilled in the art are within the scope of this invention.

CLAIMS

1. Products containing an alkylating anthracycline of formula Ia or Ib:



Ia



Ib

and a recombinant humanized anti-HER2 antibody as a combined preparation for simultaneous, separate or sequential use in antitumor therapy.

2. Products according to claim 1, wherein the recombinant humanized anti-HER2 antibody is the recombinant humanized monoclonal antibody anti-HER2 trastuzumab.

3. Products according to claim 1 or 2, wherein the alkylating anthracycline is 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin.

4. Products according to any one of claims 1 to 3, wherein the antitumor therapy is for treating cancers over-expressing HER2 protein.

5. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient and, as active ingredient, an alkylating anthracycline of formula Ia or Ib as defined in claim 1 and a recombinant humanized anti-HER2 antibody.

6. A pharmaceutical composition according to claim 5 wherein the recombinant humanized anti-HER2 antibody is the recombinant humanized monoclonal antibody anti-HER2 trastuzumab.

7. Use of an alkylating anthracycline of formula Ia or Ib as defined in claim 1 and a recombinant humanized anti-HER2 antibody in the preparation of a medicament for use in the treatment of tumors, wherein the alkylating anthracycline and the recombinant humanized anti-HER2 antibody are administered simultaneously, separately or sequentially.

8. Use according to claim 7 wherein the recombinant humanized anti-HER2 antibody is the recombinant humanized monoclonal antibody anti-HER2 trastuzumab.

9. Use of an alkylating anthracycline of formula Ia or Ib as defined in claim 1 and a recombinant humanized anti-HER2 antibody in the preparation of a medicament for use in the prevention and/or treatment of tumor metastasis, wherein the alkylating anthracycline and the recombinant humanized anti-HER2 antibody are administered simultaneously, separately or sequentially.

10. Use according to claim 9 wherein the recombinant humanized anti-HER2 antibody is the recombinant humanized monoclonal antibody anti-HER2 trastuzumab.

11. A method of treating a mammal, including a human, suffering from a neoplastic disease comprising administering to said mammal an alkylating anthracycline of formula Ia or Ib as defined above and a recombinant humanized anti-HER2 antibody, in amounts effective to produce a synergistic antineoplastic effect.

12. A method according to claim 11, wherein the recombinant humanized anti-HER2 antibody is the recombinant humanized monoclonal antibody anti-HER2 trastuzumab.

13. A method for lowering the side effects caused by antineoplastic therapy with an antineoplastic agent in a mammal, including a human, in need thereof, the method comprising administering to said mammal a combined preparation comprising an alkylating anthracycline of formula Ia or Ib as defined above, and a recombinant humanized anti-HER2 antibody, in amounts effective to produce a synergistic antineoplastic effect.

14. A method according to claim 13, wherein the recombinant humanized anti-HER2 antibody is the recombinant humanized monoclonal antibody anti-HER2 trastuzumab.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/05425 A2

(54) Title: COMBINED PREPARATIONS COMPRISING ANTITUMOR AGENTS

(57) Abstract: There are provided the combined use of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin or 4-demethoxy-N,N-bis(2-chloroethyl)-4'-methansulfonyl daunorubicin and a recombinant humanized anti-HER2 antibody, preferably trastuzumab, in the treatment of tumors and the use of said combination in the treatment and/or prevention of tumor metastasis.

We (I) hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

(Application Number) (Filing Date)

(Application Number) (Filing Date)

We (I) hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

Application Serial No.	Filing Date	Status (pending, patented, abandoned)

And we (I) hereby appoint: Norman F. Oblon, Reg. No. 24,618; Marvin J. Spivak, Reg. No. 24,913; C. Irvin McClelland, Reg. No. 21,124; Gregory J. Maier, Reg. No. 25,599; Arthur I. Neustadt, Reg. No. 24,854; Richard D. Kelly, Reg. No. 27,757; James D. Hamilton, Reg. No. 28,421; Eckhard H. Kuesters, Reg. No. 28,870; Robert T. Pous, Reg. No. 29,099; Charles L. Gholz, Reg. No. 26,395; Vincent J. Sunderdick, Reg. No. 29,004; William E. Beaumont, Reg. No. 30,996; Robert F. Gnuse, Reg. No. 27,295; Jean-Paul Lavalleye, Reg. No. 31,451; Stephen G. Baxter, Reg. No. 32,884; Robert W. Hahl, Reg. No. 33,893; Richard L. Treanor, Reg. No. 36,379; Steven P. Weihrouch, Reg. No. 32,829; John T. Goolkasian, Reg. No. 26,142; Richard L. Chinn, Reg. No. 34,305; Steven E. Lipman, Reg. No. 30,011; Carl E. Schlier, Reg. No. 34,426; James J. Kulbaski, Reg. No. 34,648; Richard A. Neifeld, Reg. No. 35,299; J. Derek Mason, Reg. No. 35,270; Surinder Sachar, Reg. No. 34,423; Christina M. Gadiano, Reg. No. 37,628; Jeffrey B. McIntyre, Reg. No. 36,867; Paul E. Rauch, Reg. No. 38,591; William T. Enos, Reg. No. 33,128; and Michael E. McCabe, Jr., Reg. No. 37,182; our (my) attorneys, with full powers of substitution and revocation, to prosecute this application and to transact all business in the Patent Office connected therewith; and we (I) hereby request that all correspondence regarding this application be sent to the firm of OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P.C., whose Post Office Address is: Fourth Floor, 1755 Jefferson Davis Highway, Arlington, Virginia 22202.

We (I) declare that all statements made herein of our (my) own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

100

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28 January 2002
Date

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Date

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300 Michele Caruso
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400 Antonino Suarato
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Antonino Suarato
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Date

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Citizen of: Italy

Post Office Address: The same as above

NAME OF FIFTH JOINT INVENTOR

Signature of Inventor

Date

Residence:

Citizen of:

Post Office Address:

Declaration, Power Of Attorney and Petition

WE (I) the undersigned inventor(s), hereby declare(s) that:

My residence, post office address and citizenship are as stated below next to my name,

We (I) believe that we are (I am) the original, first, and joint (sole) inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled

COMBINED PREPARATIONS COMPRISING ANTITUMOR AGENTS

the specification of which

☐ is attached hereto.

☐ was filed on _____ as

Application Serial No. _____

and amended on _____.

☒ was filed as PCT international application

Number PCT/EP00/06540

on 10 July 2000,

and was amended under PCT Article 19

on _____ (if applicable).

We (I) hereby state that we (I) have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We (I) acknowledge the duty to disclose information known to be material to the patentability of this application as defined in Section 1.56 of Title 37 Code of Federal Regulations.

We (I) hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed. Prior Foreign Application(s)

Application No.	Country	Day/Month/Year	Priority Claimed
9917012.8	Great Britain	20 July 1999	☒ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No